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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/605,452	09/30/2003	William G. Kerr	1372.79.PRC	2451
23557	7590	08/09/2005	EXAMINER	
SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO BOX 142950 GAINESVILLE, FL 32614-2950			HAMA, JOANNE	
		ART UNIT		PAPER NUMBER
				1632

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/605,452	KERR ET AL.
	<b>Examiner</b> Joanne Hama, Ph.D.	<b>Art Unit</b> 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 19 May 2005.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 29-41 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 29-41 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input checked="" type="checkbox"/> Other: _____                         |

## DETAILED ACTION

Applicant's response to the First Action on the Merits was filed May 2, 2005.

Claims 1-28 have been cancelled. Claims 29-41 have been added.

Claims 29-41 are under consideration.

### *Specification*

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

Figures 2, 3, and 7 comprise sequences and all are missing SEQ ID NOS.

Applicants must assign SEQ ID NOS. to each of these sequences. The SEQ ID NOS must be indicated in the figures or in the figure legends. Additionally, the SEQ ID NOS must be provided in computer readable format and in a paper listing. A statement indicating that the computer readable format and paper listing are the same must also be included.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

It is noted that Applicant has indicated 10 sequences in the specification (specification, paragraphs 21-25). It is also noted that Applicant has submitted a sequence listing (April 23, 2004). However, it is unclear whether the sequences listed in the specification are the ones provided on the sequence listing. In addition to this, with regards to the specification indicating that there are 10 sequences, these sequences must be indicated in the proper format of SEQ ID NO.

In addition to the sequence compliance, the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Paragraph 33 of the specification contains a hyperlink.

**Maintained Rejections**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-41 remain rejected in modified form under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record discussed in the Office Action of November 29, 2004.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention is drawn to a method of inducing proliferation of human or mouse stem cells comprising introducing an inhibitor of murine s-SHIP or human s-SHIP activity. The claimed invention also comprises inducing the stem cells to differentiate. However, the specification does not provide any guidance to the artisan how to induce proliferation and differentiation in any human or mouse stem cell.

The specification teaches that that the mouse TL1 ES cell line, and the ES cell lined from TL1, E10, were used. The specification also teaches that mouse B-cell lines WEHI-231, 70Z/3, A20, and BAL17 were used. The specification teaches that Hepa1-6, a mouse hepatoma epithelial cell line and 293T, a human kidney cell line were used (specification, parag. 27). The specification also teaches that cells from adult bone marrow (ABM) and fetal livers (FL) from C57BL/6 mice were used. The specification teaches that FACS was used to sort out hematopoietic stem cells (HSCs), B-lymphoid cells, and myeloid, and erythroid cells (specification, parag. 31). While the specification provides these teachings, nothing in the specification provides guidance for using any human stem cells. The specification teaches that mouse ES cells and hematopoietic cells obtained from the fetal liver and bone marrow of mice expressed a species of SHIP, s-SHIP, whereas, differentiated cells such as B-lymphocyte cell lines 70Z/3, A20, BAL17 and lineage-committed cells from fetal liver and bone marrow did not (specification, parag. 56 and 59). The specification teaches that embryonic stem cells electroporated with anti-SHIP shRNA exhibited a reduced expression of s-SHIP protein (specification, parag. 71, see also Figure 8). While the specification teaches that s-SHIP protein expression is reduced following the introduction of anti-SHIP shRNA, the

specification does not teach that introduction of anti-SHIP shRNA results in proliferation of any stem cells. Further, the claimed invention further comprises that the stem cells differentiate. With regards to this issue, nothing in the specification teaches that any stem cells differentiate into any cell type. Because the specification does not provide this guidance, the specification does not enable an artisan to practice a method of inducing proliferation of human or mouse stem cells comprising administration of an inhibitor of murine s-SHIP activity or human s-SHIP activity, and a method further comprising differentiation of human or mouse stem cells.

In addition to the specification not teaching that ES cells and hematopoietic cells proliferate and differentiate upon introduction of anti-SHIP shRNA, post-filing art teaches that mice comprising a disruption in SHIP have defects in hematopoietic proliferation. Helgason et al. 2003, Blood, 102: 3541-3547, see IDS, teach that when irradiated Pep3b mice receive transplants of various repopulating doses of bone marrow cells from SHIP<sup>+/+</sup> or SHIP<sup>-/-</sup> mice, the frequency of donor-derived cells in the recipients of SHIP<sup>-/-</sup> bone marrow cells was significantly lower than in recipients of SHIP<sup>+/+</sup> cells at 16 weeks after transplantation at all cell doses used (Helgason, page 3543, 1<sup>st</sup> col., 2<sup>nd</sup> parag. under "Impaired repopulation by SHIP<sup>-/-</sup> bone marrow cells"). Thus, the teachings of Helgason et al. do not support enablement of the claimed invention.

The specification teaches that administration of anti-SHIP shRNA was used to reduce the expression level of s-SHIP protein (specification, parag. 71). While the specification provides this teaching, the specification does not teach an artisan how to

make any anti-SHIP shRNA. The art teaches that making any shRNA is not intuitive. Jen and Gewirtz, 2000, Stem Cells, 18: 307-319 teach that while antisense interference methods appear impeccable in theory, many additional considerations must be taken into account in applying the strategy in living cells. One additional consideration is that mRNA transcripts exit in low energy conformations in which secondary structures dominate in folding the linear polymer. In addition, interactions with cytoplasmic proteins produce further structural properties. The end result is that much of the mRNA sequence is hidden and only partial sequences within the total mRNA length are accessible for hybridization. RNA folding programs that generate three-dimensional folding patterns based on free energy calculations often give an unreliable depiction for in vivo relevance (Jen and Gewirtz, page 313, 1<sup>st</sup> col., parag. under "mRNA Site Selection"). Thus, with regards to making anti-SHIP shRNA, the specification does not provide guidance to the artisan and thus the specification does not enable the artisan to make anti-SHIP shRNA, nor does the specification teach that administration of anti-SHIP shRNA result in stem cell proliferation and differentiation.

The claimed invention encompasses a method of inducing proliferation of human or mouse stem cells comprising introducing any inhibitor of murine s-SHIP or human s-SHIP activity in stem cells. In addition to sh-RNA, this encompasses the use of a dominant negative s-SHIP protein and a chemical compound. However, nothing in the specification provides any guidance as to how to make any dominant negative s-SHIP protein or any chemical compound that inhibits s-SHIP protein.

The claimed method encompasses any stem cell. In addition to ES cells and hematopoietic stem cells, the claimed invention encompasses any stem cell, including neuronal stem cells and osteoblastic stem cells. However, the specification does not teach that administration of anti-SHIP shRNA results in any proliferation and subsequent differentiation of neuronal or osteoblastic stem cells.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

#### ***Response to Arguments***

Applicant's arguments filed May 2, 2005 have been fully considered but they are not persuasive.

With regards to the Applicant's argument that RNAi has been demonstrated to facilitate gene silencing in a variety of cell types and animal models (Applicant's response, pages 5-8), the Examiner does not find the Applicant's argument persuasive because while the Applicant directs the Examiner to many example of which the art teaches successful examples of RNAi, the nothing in the specification, art, or Applicant's argument provides guidance as to how an artisan would make shRNA/RNAi against s-SHIP RNA. While the applicant points to Rohrschneider et al. (Applicant's response, page 6) to teaching the sequence of various SHIP isoforms, and that due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a gene target gene and nucleic acid

sequences that interfere with the expression of the target gene, the Applicant does not provide guidance as to how to overcome the hurdles in generating functional shRNA/RNAi. As stated above in the teachings by Jen and Gewirtz, making shRNA/RNAi is not routine in the art due to target accessibility of the target mRNA being folded into secondary structures and due to proteins bound to the mRNA. Because the Applicant has not provided guidance as to overcome these issues, an artisan does not know how to generate any shRNA/RNAi against s-SHIP. As such, the art teaches that generation of shRNA/RNAi against s-SHIP would need to be determined empirically. The Applicant points to Agrawal et al., page 671, paragraph bridging the first and second columns (Applicant's response, page 7, 1<sup>st</sup> parag.). Aragwal et al. (2003, Microbiology, and Molecular Biology Reviews, 67: 657-685) is used to argue that there are summaries of criteria for selection of interfering RNA and target mRNA sequence. With regards to this, the teachings of Agrawal, et al. do not support the Applicant's argument. Agrawal et al. teach that artisan have analyzed several parameter for optimizing siRNA-induced gene silencing. The efficacy of these parameters has been tested, but no concensus on choosing the siRNA has evolved. Thus, even in 2003, the art teaches that making RNA for gene silencing is not predictable. As such, the specification and art does not teach how to predictably make any shRNA against s-SHIP.

With regards to whether art and specification provides an artisan enough guidance such that an artisan can obtain proliferating stem cells and proliferating and differentiating stem cells upon introduction of anti-SHIP shRNA (Applicant's response,

page 8-10), the above discussion is focused on the fact that no guidance was provided such that an artisan would obtain any proliferating stem cells or any proliferating and differentiating stem cells upon introduction of anti-SHIP shRNA. Nothing in the specification indicates that the stem cells do proliferate, and nothing in the specification teaches that the stem cells differentiate. No guidance was provided as to what the proliferating stem cells differentiate into. While the Applicant points to scientific literature that teach differentiation of stem cells into various mature cell types in vitro and in vivo (Applicant's response, page 9), the Applicant does not teach that reduction of s-SHIP is responsible for the differentiation of stem cells. According to the teachings of the Examples in the specification, while there is a correlation between the expression of s-SHIP expressed in ES cells and no expression of s-SHIP in differentiated B-lymphocyte cells, nothing in the specification teaches that the reduction of s-SHIP is the reason why ES cells differentiate into B-lymphocytes (specification, parag. 56, see also Figure 3). No guidance was provided as to how an artisan would practice the claimed invention knowing that reduction of s-SHIP expression would be a viable way of inducing differentiation in ES cells.

Claims 29-41 remain rejected in modified form under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record stated in the Office Action, November 29, 2004.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at <http://www.uspto.gov/web/menu/current.html#register>).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

While the specification teaches that an anti-SHIP shRNA was used to reduce expression of s-SHIP in mouse ES cells, the specification fails to adequately describe what this anti-SHIP shRNA is and also fails to teach other nucleic acid sequences which function as anti-SHIP shRNA. In addition to this, the specification fails to adequately describe anti-SHIP shRNA which has the ability to induce proliferation in any stem cell. With regards to dominant negative SHIPs, nothing in the specification teaches any

proteins used as dominant negative SHIPs and nothing in the specification provides any guidance as to how an artisan would generate any dominant negative SHIPs. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

In the instant case, while the specification teaches one example of an anti-SHIP shRNA, which, upon introduction to ES cells results in reduction of SHIP protein expression, the specification does not teach what the sequence of anti-SHIP shRNA is. The claimed invention encompasses any anti-SHIP shRNA that inhibits expression of human s-SHIP and any dominant negative SHIP that inhibits s-SHIP activity in stem cells. However, the specification does not disclose any sequence of anti-SHIP shRNA that was used to reduce expression of human s-SHIP or any dominant negative SHIP which was used to inhibit s-SHIP activity. An artisan cannot envision the particular structure of any shRNA compound that can target any 5' UTR, any coding region, or any 3' UTR of any nucleic acid encoding s-SHIP from mouse or human that corresponds with the function of being a shRNA that inhibits the expression of any s-SHIP gene that would be commensurate with the breadth of the broad genera of anti-

SHIP shRNA or oligonucleotides as claimed. An artisan also cannot envision any particular structure of any dominant negative of SHIP such that the protein functions to inhibit s-SHIP. Neither the specification nor the prior art searched provides or points to a specific structure of an shRNA compound or oligonucleotide of the invention, that corresponds with the function of being an anti-SHIP shRNA as claimed. Further, the art and specification do not teach any dominant negative SHIP protein that inhibits the activity of human or mouse s-SHIP. The specification does not disclose any particular species of the invention, fails to disclose a representative number of species of the broad genera of shRNA compounds or oligonucleotides targeted to s-SHIP, or any proteins that are dominant negative SHIPs as claimed and does not provide any distinguishing identifying characteristics of the genera as claimed that would indicate that applicant was in possession of the broadly claimed genera. Additionally, the specification provides no guidance as to how an artisan would know the structure of additional species of the invention based on the disclosure therein. The specification, therefore, does not provide an adequate written description of the genera of antisense compounds or oligonucleotides as claimed or any dominant negative proteins, which would indicate that Applicant was in possession of said genera. Additionally, the disclosure of the specification provides no specific guidance as to how an artisan might be reasonably led to a particular species of the invention that would function commensurate with the scope what is now claimed.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*,

25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no anti-SHIP shRNA meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

#### ***Response to Arguments***

Applicant's arguments filed May 2, 2005 (Applicant's response, page 10-13) have been fully considered but they are not persuasive.

With regards to the Applicant's response that there is sufficient written description of the claimed subject matter, the Examiner disagrees. While the Applicant argues that the art teaches the mRNA sequence of mouse s-SHIP and human s-SHIP (SIP-110), and that an artisan due to certainty of the genetic code and complementarity of bases, would know how to generate a shRNA against sSHIP, the Examiner disagrees with the Applicant's argument. As taught by Agrawal et al, and Jen and Gewirtz, the making of any gene silencing RNA is unpredictable. No guidance was provided by the specification as to what structure of shRNA was used to reduce expression of s-SHIP,

as shown in Figure 8. As the specification and art do not provide this guidance, there is no written description for any anti-SHIP shRNA.

### ***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

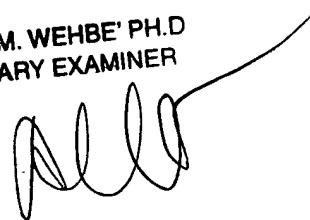
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JH

ANNE M. WEHBE, PH.D.  
PRIMARY EXAMINER

ANNE M. WEHBE, PH.D.  
PRIMARY EXAMINER



**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
7. Other: \_\_\_\_\_

**Applicant Must Provide:**

- An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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